DETAILED ACTION

1. The Office Action mailed 1/08/08 has been vacated. A corrected Office Action follows. The reply period for this Office Action will start from the mailing date of this communication.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/11/2007 has been entered. An action on the RCE follows.

3. Claims 1, 25, 32 and 43 have been amended. Claims 1, 3, 11, 25, 27-30, 32-39, 43 and 44 are pending and examined.

4. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

5. Applicant has alleged that a declaration was submitted by Dr. Pamela McCombe with the response of October, 2006. However, there is no record of a declaration by Dr. Pamela McCombe with the response of October, 2006 (Applicant is advised to check Public PAIR).

Claim Rejections - 35 USC § 103, maintained

6. The rejection of claims 1, 3-11, 25, 27-30 ad 32-39 and 43-44 under 103(a) as unpatentable over Morton et al. (WO 95/15338) in view of the M.S. study (Neurology,

1993) is maintained for reasons of record in the Office Actions dated 5 August 2003, 5 October 2004, 27 April 2005, 1 February 2006 and 16 June 2006 and 19 January 2007.

The claims require treating multiple sclerosis by administering cpn10 and IFN-β, wherein the therapeutic effect of administering cpn10 and a clinically ineffective amount IFN-β together is improved compared to therapeutic effect of administering the same equivalent amount of cpn10 or IFN-β alone. Applicants assert that neither the Morton reference nor the MS study, nor the combination thereof, teaches or suggests that combined cpn10 and IFN-β treatment of MS or delay the relapse following cessation of other treatments. Applicant's arguments have been fully considered but are not found to be persuasive.

Applicant has modified the claims to include IFN-β amounts that are clinically ineffective amount. Applicant asserts that the invention provides methods of treating MS in an individual taken off IFN-β treatment or having reduced dose IFN-β treatment because of IFN-β-induced side effects, by administering to an individual in need thereof a combination treatment comprising pharmaceutically effective amounts of both cpn10 and IFN-β, wherein the IFN-β is administered at a dose that does not produce IFN-β induced side effects in the individual. As argued previously in the Office Action dated 6/16/2006 (pages 4-5) the dosages of cpn10 and IFN-β disclosed in Morton et al. and the MS study are within the doses contemplated in the instant invention. For example, Morton on page 27 discloses cpn10 doses of 1-1000μg/kg of body weight and more preferably 50-200μg/kg of body weight encompasses the 10-30 mg of cpn10 contemplated in the instant invention. In addition, the IFN-β doses disclosed in the MS

study group (1.6 MIU and 8 MIU) are similar to those contemplated in the instant invention.

Applicant argues that administering a drug at dosages, which, if not administered in combination with a second, different drug, would be ineffective (clinically), is a significantly different fact pattern than "optimizing" an otherwise clinically effective dose at dosages. Applicant further contends that administering a drug at a clinically ineffective dose is not merely "optimizing a workable range" by routine experimentation. The MS study group used 1.6MIU and 8MIU, which is within the "clinically ineffective dose" contemplated by the Applicant (1-10MIU). Furthermore, the 1.6MIU of IFN-β used in the MS study is much lower than 4-6MIU recited in the claims and less than optimum compared to 8MIU administration (page 660). The MS study also discloses that 16MIU produced unacceptable toxicity (page 660). Therefore, *In re Aller* fact pattern is applicable to the administration of IFN-β because it is routine in the art to optimize the dosage administered to a patient obtain optimal clinical outcome and thus not inventive. Furthermore, contrary to Dr. Johnson's declaration (As indicated above in paragraph 5 there is no declaration from Dr. Pamela McCombe is of record) and argued by the Applicant that there was no understanding or teachings in the art at the time of the invention to lower an otherwise toxic and clinically ineffective dose of IFN-β and then combine the dose with cpn10 to realize an effective therapy for MS, the MS study clearly discloses reduced doses of IFN-β to reduce the toxicity. This in combination with Morton's teaching will make the instant invention obvious over prior art.

Applicant asserts on page 11 that Jeffrey et al. (2004) teaches away from instant invention. This has been previously addressed by the Office in the Office Action mailed 2/1/2006 pages 5-6. Although, Applicant sites Jeffrey to argue that (quoting Jeffrey) "the agent added to the primary therapy may have no effect, or worse, may antagonize the effect of the primary agent". However, the complete reading of the article does teach away from combination therapy and suggests that studies are needed to address the question of whether there is an additive or synergistic effect and to address the long-term safety of the combination.

In addition, Applicant contends that Morton (1998) and Yu et al. (1996) also teach away from the instant invention because Johnson declaration claims that the cpn10 and IFN-β taught by the references acted against MS via similar immunosuppressive mechanisms. Thus, it is asserted that a practitioner in the field would not have expected that combination of drugs having similar mechanisms would have any co-operative effect. Applicant's arguments regarding mechanism of action have been noted. Although, the end result of the treatment with cpn10 and IFN-β as reported by Morton (1998) and Yu et al. (1996) appears to be the same (T cell proliferation and DTH reaction), both the cpn10 and IFN-β would be expected act by different mechanisms because these two different cytokines bind different receptors. Further, In re Kerkhoven (205 USPQ 1069, CCPA 1980) summarizes:

> "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art."

Thus, contrary to Dr. Johnson's declaration, at the time of the invention a skilled artisan would have been able to predict a therapeutic effect upon the combined administration of cpn10 and IFN-β in treating MS.

Applicant also is arguing that Barbero et al. (2004) teaches away from the present invention because Barbero et al. disclose that patients who took IFN-β at higher doses and frequency had better clinical out come compared to those who did not. The doses recommended by the Barbero reference (8 MIU (250 µg) administered ever other day are identical to those recommended by M.S study group (1993) which is similar to those contemplated by the instant invention. This is in contrast to the lower dose 6MIU (30 µg) that is administered once a week (lower dose). Therefore, there is no evidence to "teach away" from the present invention.

Arnason and Durelli references sited by the Applicant disclose IFN-β doses that is identical to the dose used M.S study group (1993) which is similar to those contemplated by the instant invention. Therefore, there is no evidence to "teach away" from the present invention.

In addition, Applicant asserts that *in re Kerkhoven* is Applicable to the instant fact pattern because "clinically ineffective" dose of IFN-β was not taught in the prior art. This is not found to be persuasive because the doses contemplated in the instant invention (1-10MIU) are all taught by the prior art of record including M.S study group (1993), Barbero et al. (2004), Arnason (2005) and Durelli (2005). Therefore the rejection of record is maintained.

7. New rejections necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 112, second paragraph (New)

8. Claims 1, 25, 32, 43 and 44 are rejected as vague and indefinite for reciting the term "clinically ineffective" is not defined in the specification. The artisan would be unable to determine what amounts Applicants intended the claims to encompass. Is the pharmaceutically effective amount different from the clinically ineffective amount? Claims 3-11, 27-30 and 33-39 are rejected insofar as they are dependent on rejected claim 1.

Claim Rejections - 35 USC § 112, first paragraph (New)

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-11, 25, 27-30 ad 32-39 and 43-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

The recitation of "clinically ineffective or not be clinically effective" has no support in the specification. Although Applicant in the response filed 10/11/07 (page 8) indicates that the support for the claim language is found at page 13, lines 3-6, the disclosure at

page 13, lines 3-6 discloses that IFN-β might be ineffective or sub-optimal. There is no disclosure of clinically ineffective amounts. The Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

10. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao, Ph. D can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JS
January 24th, 2008

/Jegatheesan Seharaseyon, Ph.D/

Primary Examiner, Art Unit 1647